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FULL-LENGTH ORIGINAL RESEARCH

The prevalence of atypical presentations and comorbidities of benign childhood epilepsy with centrotemporal spikes

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Summary

Purpose: Benign childhood epilepsy with centrotemporal spikes (BCECTS) is the most common epileptic syndrome in childhood. The outcome is usually excellent, but there are some atypical forms of BCECTS with less favorable outcomes. The aim of this study was to delineate the frequency of these atypical features among patients with BCECTS.

Methods: We conducted a retrospective chart study by retrieving the medical records of all consecutive patients with BCECTS who were evaluated in four pediatric neurology outpatient clinics in Israel between the years 1991 and 2008.

Key Findings: A total of 196 patients with BCECTS were identified (78 female and 118 male; mean age at time of diagnosis 7.64 years, range 1.5–14). The mean duration of follow-up was 4.43 years (range 2–11). Nine patients (4.6%) developed electrical status epilepticus in slow waves sleep (ESES) during follow-up, four (2%) had Landau-Kleffner syndrome, three (1.5%) had BCECTS with frequent refractory seizures, two (1%) had BCECTS with falls at presentation, one (0.5%) had a ''classic'' atypical variant, and one (0.5%) had oromotor dysfunction. None had rolandic status epilepticus. Sixty-one patients (31%) had attention deficit hyperactivity disorder (ADHD), 43 (21.9%) had specific cognitive deficits, and 23 (11.7%) had behavioral abnormalities, including aggressiveness, anxiety disorders, depression, and pervasive developmental disorder (PDD).

Significance: The prevalence of most atypical forms of BCECTS other than ESES is low. There is, however, a high prevalence of ADHD and specific cognitive deficits among patients with BCECTS.

KEY WORDS: Rolandic, Centrotemporal, Electrical status epilepticus sleep, Landau-Kleffner, Atypical, Attention deficit hyperactivity disorder.

Benign childhood epilepsy with centrotemporal spikes (BCECTS) was originally described by Martinus Rulandus in 1597 (Van Huffelen, 1989). The syndrome is sometimes called rolandic epilepsy because of the characteristic features of partial seizures involving the region around the lower portion of the Rolandic fissure. BCECTS is the most frequent of the benign focal epilepsies of childhood and represents 15–25% of epilepsy syndromes in children younger than 15 years of age (Fejerman et al., 2007). The age at onset ranges from 3–13 years, with the peak incidence occurring between the seventh and eighth years of life (Kriz & Grazdik, 1978). BCECTS is seen more in male patients, with a male-to-female ratio of 3:2 (Fejerman et al., 2007).

The seizures are characterized by hemifacial motor seizures and may be preceded by somatosensory symptoms involving the inner cheek, tongue, and lips (Lombroso, 1967; Aicardi, 1987). The symptoms frequently involve the hand or both the hand and leg on the side ipsilateral to the involved facial side (Loiseau & Beaussart, 1973; Aicardi, 1987). The seizures usually occur during sleep in most children, but they may also occur during the daytime. More than one half of the children with BCECTS have nocturnal seizures only (Kriz & Grazdik, 1978).

Atypical Forms

BCECTS was initially described as a benign epilepsy syndrome, but a number of studies later showed that a significant number of patients with BCECTS had some degree of neuropsychological impairment (Fejerman et al., 2007). The first description of atypical features of BCECTS was published by Aicardi & Chevrie in 1982, and it was followed by many other descriptions of atypical features during the ensuing years. The current consensus is that atypical forms of BCECTS are actually common, but there are different views regarding their frequency. The frequency is as

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low as 1–7% if only patients with Landau-Kleffner syndrome, electrical status epilepticus in slow wave sleep (ESES), and classic atypical BCECTS are considered (Panayiotopoulos, 1999; Fejerman et al., 2000). When less strict criteria are applied, however, the frequency varies substantially among different studies and ranges between 9% and 52% (Beaussart & Faou, 1978; Morooka et al., 1995; Wirrell et al., 1995; Massa et al., 2001; Verrotti et al., 2002; Datta & Sinclair, 2007). This extremely wide range is the result of different inclusion criteria, mainly involving the extent of subtle cognitive deficits. The relative frequency of the different atypical forms within the population of patients with BCECTS has not been established.

The evolution of BCECTS into ESES as well as into Landau-Kleffner syndrome (LKS) has been described previously in detail (Dalla Bernardina, 1989; Fejerman et al., 2000; Massa et al., 2000; Tassinari et al., 2005; Kramer et al., 2009).

Other atypical forms of BCECTS include benign childhood epilepsy with centrotemporal spikes with frequent refractory seizures (Lerman & Kivity, 1975; Loiseau et al., 1988; Kramer et al., 2002), the ''classic'' atypical variant of BCECTS (Aicardi & Chevrie, 1982; Fejerman et al., 2000), status epilepticus of BCECTS (Fejerman & Di Blasi, 1987), BCECTS with transient oromotor dysfunction (Roulet et al., 1989; Deonna et al., 1993; Kramer et al., 2001; Dubois et al., 2003), and BCECTS presenting as falls (Watemberg et al., 2009). The ''classic'' atypical form usually presents as severe aggravation, but in contrast to ESES and LKS, the cognitive outcome is always favorable (Fejerman et al., 2007).

Comorbidities

In addition to the atypical forms, BCECTS is frequently associated with various comorbidities including specific cognitive deficits as well as behavioral difficulties.

1 Benign childhood epilepsy with centrotemporal spikes with specific cognitive deficits (BCECTS).
Children with BCECTS were initially described as being free of neuropsychological impairments (Lerman & Kivity, 1975; Fejerman et al., 1997). However, later studies reported significant deficits in attention, visuomotor skills, and a variety of specific language skills (Rugland et al., 1987; Weglage et al., 1997; Staden et al., 1998; Croona et al., 1999; Deonna et al., 2000; Massa et al., 2001; Papavasillou et al., 2005; Holtmann et al., 2006; Goldberg-Stern et al., 2010).

2 Attention deficit and hyperactivity disorder (ADHD).
The overall prevalence of ADHD among children is 5–6% (Brown et al., 2001). An increased frequency of rolandic spikes was found in children with ADHD (Holtmann et al., 2006).

3 Behavioral and psychiatric problems.
Cohorts of children with BCECTS have been reported to display behavioral and psychiatric problems, including aggression and oppositional behavior (Yung et al., 2000). The aim of the current study was to calculate the frequency of these atypical features as well as the rate of comorbidities in a population of BCECTS patients.

Methods

Study design

The medical records of consecutive patients with BCECTS were retrieved between 1991 and 2008 from four pediatric neurology outpatient clinics in four medical centers affiliated to Tel Aviv University in Israel. The charts were retrieved according to BCECTS patient registries or selected from the electroencephalography (EEG) archives of files demonstrating an EEG pattern compatible with BCECTS. All participants were diagnosed as having epilepsy when they were between 3 and 14 years of age. Only patients with a minimal follow-up period of 2 years were included. The data that were retrospectively retrieved from the files included the age of onset of seizures, medical history, history of febrile convulsions, family members with epilepsy, findings from the neurologic examination and imaging studies, EEG abnormalities, history of secondary generalizations, response to the first antiepileptic drug (AED) defined as cessation of seizures following administration and dose increments of the drug, duration of medical therapy, duration of follow-up, the presence of seizures at follow-up, and atypical features of BCECTS.

Our main goal was to identify the patients with atypical forms of the disease. The following criteria were used to define a patient as having an atypical feature:

1 The ''classic'' atypical variant of BCECTS: a period of typical rolandic seizures followed by frequent atonic seizures that led to frequent falls, partial and generalized motor seizures, and atypical absence attacks.

2 Status epilepticus of BCECTS: events longer than 30 min of typical partial rolandic attack.

3 ESES: the presentation of epilepsy with different seizure types, neuropsychological impairment in the form of global or selective regression of cognitive functions other than behavioral or ADHD, or motor impairment, with epileptic activity density of ≥50%, either focal or generalized during slow wave, non–rapid eye movement (REM) sleep.

4 Landau-Kleffner syndrome: acquired epileptic aphasia with verbal auditory agnosia (Fejerman et al., 2007). Patients with specific acquired language deficits that were less severe were also included.

5 BCECTS with frequent refractory seizures: the occurrence of >100 seizures per year despite therapeutic trials with a number of drugs.

6 Transient oromotor dysfunction: periods of oromotor deficits characterized by facial weakness, hypersialorrhea, difficulties in chewing and swallowing, and/or reduced speech fluency with difficulties in pronunciation and articulation.
7 BCECTS presenting as falls: the initial presentation characterized by episodes of brief lapse of postural tone that caused falls without loosing consciousness, accompanied by EEG features of BCECTS.
8 BCECTS with specific cognitive deficits (other than ADHD): deficits in short-term memory, visuomotor skills, and a variety of specific language skills, including recall of auditory verbal material, auditory perception, reading comprehension, spelling, expressive grammar, and verbal fluency, which were diagnosed by a formal didactic diagnosis. Patients with a documented IQ decline or regression in speech comprehension and/or production were not included in any of the comorbidities groups.
9 ADHD: diagnosed by either a formal psychological/didactic evaluation, or clinically by questionnaires including Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) and positive response to psychostimulants. The neuropsychological tests test included Wechsler Intelligence Scale for Children-Revised and Kaufman Assessment Battery for Children.
10 Behavioral and psychiatric problems: aggression, oppositional defiant disorder, anxiety disorder, depression or pervasive developmental disorder (PDD). Except for aggression that was reported by parents, all other psychiatric diagnoses were confirmed during psychiatric evaluation.

Results

A total of 196 patients with BCECTS were identified (118 male and 78 female) in the databases of the four participating medical centers. The patients with BCECTS had been diagnosed as having epilepsy at a mean age of 7.64 years (range 1.5–14). There was a family history of epilepsy in 25 patients (12.7%). The mean duration of follow-up was 4.43 years (range 2–11). Only 12 patients (6.1%) were not seizure free at the time of the last follow-up. Seventy-eight patients (39.7%) had experienced at least one generalized tonic–clonic seizure (GTCS) throughout the years of follow-up.

Excluding the 19 patients with severe atypical forms, 46 patients were not treated, whereas the other 131 patients (74%) were treated with AEDs. Ninety-one of them (69.5%) responded to the first AED, being in most cases either carbamazepine or sulthiame, and an additional 24 (18.3%) responded to the second drug. Sixteen patients (12.5%) needed additional drugs to control their seizures.

The most common atypical feature of BCECTS in our study was ESES, which affected 9 (4.6%) of all the study patients (Fig. 1). These patients had been diagnosed as having epilepsy at a mean age of 5.4 years (range 2–8), compared with the onset age of 7.8 years of the patients with typical BCECTS. The mean duration of follow-up of the ESES patients was 5.6 years. The average time from the onset of BCECTS until the appearance of ESES was 16 months (range 0–36). Three ESES patients had frequent refractory seizures. All nine patients underwent didactic and neuropsychological evaluations. Regression was evidenced by a decline in IQ in four children, language deterioration in four, ADHD in five, aggressive behavior in three, and motor deterioration characterized by right leg progressive weakness, anxiety disorder, and autistic regression in one each. The most efficacious AED for controlling seizures was levetiracetam (received as second-line treatment after failure of another AED in five treated patients), followed by sulthiame (n = 3) and clobazam (n = 2). Six patients were also treated with steroids and intravenous immunoglobulin (IVIG). In five patients, following successful treatment there was a normalization of EEG, with only two having full clinical regaining previous cognitive level and three displaying partial improvement. Four of the ESES patients, however, still had EEG studies and deficits compatible with ESES despite treatment.

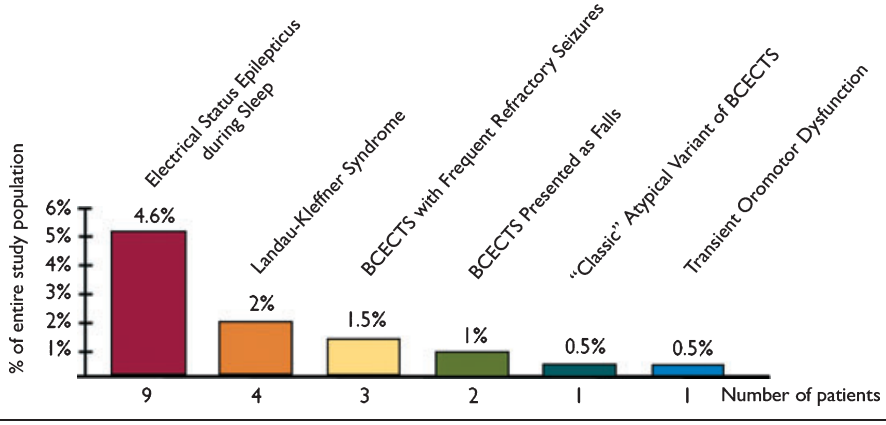

Figure 1.
The prevalence of atypical presentations of BCECTS.
Epilepsia © ILAE

All the other atypical forms of BCECTS were less common. Four patients had LKS and their age at seizure onset was 3–8 years. Except for language deterioration, three had aggressive behavior, and ADHD; and the fourth had an anxiety disorder. Their EEG studies were characteristic of LKS: two had right temporoparietal spikes with generalizations over 80% of non-REM sleep and the other two had bilateral rolandic discharges over > 40% of non-REM sleep. One LKS patient had numerous atypical absence seizures, which were refractory to >10 different anticonvulsive medications, and he also underwent a cognitive decline during a prolonged follow-up. Another LKS patient had verbal auditory agnosia that was refractory to five anticonvulsive drugs and IVIG. Improvement was achieved under pulse steroid therapy, and there was relapse when tapering was initiated. These latter two patients are now being treated with a protocol of once weekly steroid treatment. The other two patients responded to conventional AEDs (sulthiame and clobazam).

The three patients that were classified as BCECTS with frequent seizures were diagnosed as having epilepsy at a mean age of 7.1 years (range 5.5–8). They had >100 seizures per year each and required an average of three to four anticonvulsive drugs, with resolution of symptoms after an average of 4.6 years under drug therapy.

Two patients with typical EEG studies presented with falls at the ages of 20 months and 2 years and 8 months. The former had numerous fall episodes that were controlled under a regimen of three anticonvulsive drugs. This patient's condition eventually evolved to ESES. The latter had fall episodes that required second-line anticonvulsive therapy that stopped the falls. There were two more patients who had fall episodes compatible with loss of postural tone: one had a ''classic'' atypical BCESTS, whereas the other had an otherwise typical BCECTS.

One patient fulfilled the criteria for ''classic'' atypical variant of BCECTS. He presented with typical rolandic seizures at the age of 6 years and had numerous atypical absence seizures and a few fall episodes. He was also diagnosed as having Asperger syndrome and ADHD. He showed significant improvement from treatment with lamotrigine, but he was still having a few seizures per year over a period of 8 years, until there was a resolution of seizures at age 13.5 years.

One patient had transient oromotor dysfunction. He presented with seizures characterized by eye blinking, head drops, and falls at the age of 2 years and 8 months. A severe language deterioration characterized by difficulties in pronunciation and articulation was noted 1 year later. The EEG at that time demonstrated right centrotemporal rolandic spikes with generalizations over 60% of non-REM sleep. The oromotor dysfunction encountered in this specific child was observed during a period of frequent EEG discharges and was neither ictal nor postictal phenomena. There was no loss of vocabulary or speech comprehension. This child was treated with sulthiame and clobazam with significant improvement, although he did not regain baseline speech fluency. No patients in our study population fulfilled the criteria for status epilepticus of BCECTS.

A total of 23 patients (11.7%) had at least one behavioral or psychological problem. The most common behavioral problem was aggression, affecting 15 patients (7.6%). Five other patients (2.5%) had an anxiety disorder, two patients (1%) had PDD, and one had depression.

Seventeen (8.6%) of our study patients were diagnosed as having learning disabilities alone, 35 patients (17.8%) were diagnosed as having ADHD alone, and 26 patients (13.2%) were diagnosed as having both learning disabilities and ADHD. The diagnosis of learning disabilities was based on didactic and psychological evaluations in all these patients. Forty-six patients (75.4%) who were diagnosed as having ADHD underwent didactic and psychological evaluation, whereas another 15 patients (24.6%) were diagnosed by their neurologists based on neurologic evaluations and parents' and teachers' reports. Patients with ESES or LKS were excluded from this analysis.

Discussion

This is a large-scale retrospective study designed to determine the prevalence of all atypical presentations of BCECTS. A large scale was required due to the relatively low prevalence of some of the atypical features of this disorder. The demographic characteristics of our patients were the same as the previously reported ones: they were diagnosed as having epilepsy at a mean age of 7.64 years, and there was male predominance (Loiseau & Beaussart, 1973; Lerman & Kivity, 1986; Chahine & Mikati, 2006). In addition, 39.7% of our patients experienced GTCS during the years of follow-up, comparable to the 20–54% reported by others (Lerman & Kivity, 1986; Aicardi, 1987; Bauma et al., 1997; Chahine & Mikati, 2006). The average duration of medical treatment was 3.84 years, and the response to the initial therapy was excellent in most of the typical cases. These findings support the benign course of this disorder, although it emerged that the course was less favorable with regard to cognitive deficits.

The most frequent atypical feature in our study was ESES. The prevalence of 4.6% found in the current study is markedly higher than the 0.5% prevalence of ESES in all childhood epilepsies (Morikawa et al., 1989). As expected, these patients had a younger age of onset of epileptic seizures compared with the other patients in the study population. We previously reported that the rate of BCECTS patients within our series of epileptic patients with ESES was 37% (Kramer et al., 2009). The prevalence of LKS in our cohort was 2%. Patients with both syndromes were defined according to clinical criteria and EEG density disregarding quantitative EEG features (Scheltens-de Boer, 2009). The combined rates of the severe types is similar to

the 7% previously reported by Fejerman et al. (2000) and significantly higher than the 1% reported by Panayiotopoulos (1999). The rate of frequent refractory seizures accounting for 1.5% is much lower than the reported 6–18% prevalence (Lerman & Kivity, 1975; Loiseau et al., 1988; Kramer et al., 2002). This large difference is probably the result of different inclusion criteria.

Epileptic negative myoclonus may appear during the course of the disease in BCECTS patients. We separated the patients with epileptic negative myoclonus who presented with falls from the patients with classic rolandic seizures and falls and the patients who had falls as part of ''classic'' atypical BCECTS: this selection yielded only two patients (1%) in our study population. We believe, however, that some of these children are misdiagnosed as being clumsy, and that the true prevalence of this atypical feature is higher. This unrecognized form of presentation of epileptic negative myoclonus was recently published by our group (Watemberg et al., 2009).

Only one patient in our current series displayed symptoms compatible with the characteristics of the ''classic'' atypical variant of BCECTS, and only one patient had transient oromotor dysfunction.

The percentage of our BCECTS patients with ADHD in our study was 31%, compared to the rate of 11% reported by Datta and Sinclair (2007) and the 5–6% prevalence among children globally (Lerman & Kivity, 1986). The underlying mechanisms of ADHD in epilepsy remain to be studied.

Our findings also support previously published articles that claimed that BCECTS is not benign in terms of cognitive deficits (Rugland et al., 1987; Weglage et al., 1997; Staden et al., 1998; Croona et al., 1999; Deonna et al., 2000; Massa et al., 2001; Papavasillou et al., 2005; Holtmann et al., 2006; Danielsson & Petermann, 2009; Goldberg-Stern et al., 2010). Up to 21.8% of the patients in our cohort were diagnosed as having cognitive deficits, similar to the findings of Yung et al. (2000) in a smaller cohort of BCECTS patients.

As for psychiatric and behavioral problems, 11.7% of our patients had behavioral problems, especially aggressiveness, whereas 3% had anxiety disorders or depression and 1% had PDD. These numbers are higher than the prevalence of these phenomena in the general pediatric population but lower than the prevalence observed among children with other epilepsies (McDermott et al., 1995; Davies et al., 2003).

In summary, this is a large-scale study designed to determine the prevalence of the atypical features of BCECTS, both malignant and nonmalignant. The accumulated data demonstrated that there was a very low prevalence of the malignant atypical features of BCECTS, other than ESES. They also showed a high prevalence of ADHD and cognitive deficits among children with BCECTS. The main contribution of this study is the observation of an unexpectedly high rate of evolution into ESES, which underlies cognitive deterioration in this otherwise benign epileptic syndrome. A prospective study is needed to define the clinical spectrum and the comorbidities of patients with BCECTS.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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